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DEPENDENCE OF THE EFFECT OF IONIZING RADIATION ON THE COURSE OF VIRAL INFECTIONS ON THE DOSE OF VIRUSES USED FOR THE INFECTION OF ANIMALS

/Following is the translation of an article by A. G. Moroz and O. P. Peterson, Institute of Virology imeni D. I. Ivanovskogo, AMN, USSR, Moscow, published in the Russian-language periodical Voprosy Virusologii (Problems of Virology), No 5, 1967, pages 562-566. It was submitted on 18 Oct 1966./

It has been demonstrated in many works that the influence of ionizing radiation on the course of experimental viral infection depends on the dose and the time of irradiation (before and after infection), on the period between irradiation and infection, pathogenesis of the infection, etc. /8, 17, 18, and others/. However, up until now it is still not clear why under approximately the same experimental conditions some authors establish a negative and others a positive effect of irradiation *. For example, X-ray irradiation with a dose of 100 R, conducted 48 hours prior to infection of white mice with the influenza virus, according to data of some authors /13, 22/ causes a lowering, and according to data of others /18/ an increase in the susceptibility of animals to this virus. Cases of a positive and negative effect of radiation on the course of viral infection have also been described for X-ray irradiation with doses less than 100 R /1, 11, 16, 18, 22/. We have attempted to explain the reason for such a difference in the effect of radiation.

* A negative effect of ionizing radiation is expressed in an increase in the number of animals which died from infection, and a positive effect - by a lowering of this index.

Of the number of conditions in carrying out an experiment which could exert and influence on the nature of the action of X-ray irradiation, we gave special attention to the dose of virus used for infection of the animals.

Positive Action of X-ray Irradiation and Dose of Viruses

Dubin and associates /22/ showed that X-ray irradiation with a dose of 100 R, conducted 48 hours prior to the infection of white mice with the virus of swine influenza, lowered the susceptibility of the animals to infection with this virus. At this dose of virus almost 100% death of animals (15 out of 16) was observed in the control group (nonirradiated mice).

According to data from Rowe /27/ after total X-ray irradiation of adult mice with a dose of 300 R, conducted 1 and 4 days (but not 6 days) prior to the intracerebral or intraperitoneal injection of

the lymphocytic choriomeningitis virus, the survival rate increases noticeably and there are less objective proofs of the presence of infection. In the control (nonirradiated) animals viral infection caused 100% death.

Ye. I. Sklyanskaya [17] established that X-ray irradiation (75, 200, 300, and 500 R), performed 2 days after the intracerebral infection of mice with the Dakar strain of the yellow fever virus, produces a significant lowering in the susceptibility of the irradiated animals to the virus (regardless of dose of irradiation) in comparison with nonirradiated. Out of 9 control animals (infected, nonirradiated) 6 died.

Goldberg and associates [24] demonstrated that if X-ray irradiation is begun 24-48 hours after intranasal experimental infection with the St. Louis encephalitis virus and was carried out with 24-hour intervals right up to the death of the mice or no longer than 12 exposures (single dose 150 R), then it has a positive influence on the course of the virus infection: in the test group 19 animals out of 38 died, and in the control - 52 out of 53.

Thus a positive effect of both preliminary (100-300 R) and subsequent (75-500 R) X-ray irradiation is observed mainly in those cases when the infecting dose of virus causes almost the 100% death of control (nonirradiated) animals.

Nature of the Action of Ionizing Radiation and Dose of Virus

It can be expected that with a reduction in the dose of virus the positive effect of X-ray irradiation will gradually transform into a negative effect.

Thus if the dose of swine influenza virus used caused the death of almost 100% of the control (nonirradiated) mice then, as was noted above [22], preliminary X-ray irradiation exerted a positive effect on the course of influenza infection. Under these same conditions [22] subsequent irradiation (5, 50, 100, or 200 R 24 hours after intranasal infection) did not influence influenza infection.

While the infecting dose of influenza virus caused the death of approximately 36-50% of control (nonirradiated) mice, preliminary X-ray irradiation with a dose larger than 200 R had (however still not constant) a tendency to increase the susceptibility of the animals to influenza infection [18, 20].

We proposed that on a model of infection caused in mice by the virus of human influenza the dependence of the nature of the effect of X-ray irradiation on the dose of the virus is manifested almost the same as on a model of infection caused in animals by the virus of swine influenza in view of the great similarity in the biological properties of both viruses.

And, finally, when the infecting dose of virus caused the death of approximately 5% of the control (nonirradiated) mice then the preliminary X-ray irradiation with doses larger than 200 R already as a rule increased the susceptibility of the animals to influenza infection [10, 15, 20].

Thus following a lowering of the dose of virus from that which causes the death of almost 100% of the control (nonirradiated) animals to doses at which almost all the animals survive in actuality a tendency is noted for the transformation of the effect of total X-ray irradiation from positive into negative. This tendency can be followed based on the results from the investigations of a number of authors.

Thus when DeGara and Furth [23] used large doses of influenza virus for infection (24-48 hours after irradiation) the percentage of sick and perished animals among mice (lines of black-agate: C_3H and IC_3H and lines of white mice : Swiss, A, and Rf) which had been irradiated with 300 R was the same as among nonirradiated mice. When these same authors used small doses of virus for infection, in irradiated mice this index was already considerably higher than in nonirradiated mice. Beutler and Gezon [20] did not detect any differences in the percentage of death of infected irradiated and nonirradiated animals if for the infection of irradiated (from 50 to 750 R) mice they used an influenza virus which had been adapted to mice (under the conditions of this experiment caused the death of 50% of the nonirradiated animals); when using a strain which was adapted to chick embryos they established a highly significant excess of this index in experimental mice (infected, irradiated) in comparison with the control (infected, nonirradiated).

This same tendency is revealed in a comparison of the data of P. I. Remezov [14] and Rowe [27]. We already noted above that if for infection of white mice a dose of lymphocytic choriomeningitis virus was used which caused the death of nonirradiated control mice without exception, then with the preliminary irradiation with a dose of 300 R the susceptibility to the virus was reduced [27] (positive effect of X-ray irradiation). If for infection they used a mild dose of virus which caused the death of approximately 50% of nonirradiated control mice (8 out of 15), then as a result in animals which were preliminarily irradiated with doses of 200, 300, 400, and 500 R the resistance to the virus was reduced in comparison with the control [14].

In the same manner [17] if for the subcutaneous and intracerebral infection of white mice they used large doses of encephalomyocarditis virus (strain MM), which causes the death of control nonirradiated mice almost without exception, then no difference was noted in susceptibility to virus between the test (preliminary

irradiation with a dose of 300 R) and the control (nonirradiated animals) groups (out of 16 test mice 16 died, and out of 15 control - 15). If the infecting dose of virus was small, then mice which had been preliminarily irradiated with a dose of 300 R, turned out to be considerably more susceptible to the virus than non-irradiated mice.

When using 100 LD_{50} of Taylor encephalitis for infection, which causes the death of the majority of white mice in the control, Tanner and Cochie [28] noted a lower mortality rate in irradiated animals than in nonirradiated. With the use of a lesser dose of virus (10 LD_{50}) for infection an increase was observed in the percentage of dead mice among those irradiated.

Analogous results were obtained also on a model of the poliomyelitis virus. Lenz and Jungeblut [26] established that X-ray irradiation did not exert any effect on the course of poliomyelitis in monkeys. The percentage of dead control (nonirradiated) animals was close to 100. *

* The authors present information only about the dead experimental animals (6/7). However, if it is considered that an effect of X-ray irradiation on the course of the infectious process was not detected, then the number of dead control monkeys apparently was hardly any different from that in the test group and, consequently, was approximately equal to 6/7.

Other authors [19], who in their experiments used a dose of poliomyelitis virus at which almost all the control (nonirradiated) monkeys survived, noted that in test animals (irradiated, infected) there was a significant increase of susceptibility to the virus in comparison with the control (nonirradiated, infected).

In all, what has been stated makes it possible to draw the following general conclusion: with a decrease in the dose of virus an *2 aggravating effect *3 of radiation on the virus infection process is exposed, and conversely with an increase of dose of virus *2 a "medicinal" effect of radiation *4 on the virus infection process is revealed.

*2 Expressed in percentages of dead control (nonirradiated, infected) animals.
*3 The percentage of dead animals is increased.
*4 The percentage of dead animals is reduced.

The results of our experiments [9] with the virus of epidemic parotitis are also contained in the regularity noted above. The virus of parotitis does not cause the death of laboratory animals, therefore due to the presence of the low pathogenicity of the virus for white mice and guinea pigs it could be expected that there would be an increase in their susceptibility *3 to the virus as a

result of irradiation. And in actuality in 2 out of 3 tests on guinea pigs, which were irradiated with 300 R and infected, a statistically significant increase was observed in the frequency of cases of death in comparison with the control (irradiated, noninfected).

In the hypothetical explanation of the dependence between the effect of irradiation and the dose of virus we proceeded from investigations which demonstrated: a) suppression, by X-ray irradiation, of the infiltrative-inflammatory component of the response reaction of the organism to the virus [2, 3, 5, 6, 14, 17]; b) a strengthening, as a result of irradiation, of destructive changes in cells in which the viruses multiply [3, 7, 17, 25, 26]; c) histological changes in a large number of cells, which are susceptible to the virus, as a result of exposure to radiation [2]; and d) increase in the permeability of tissues of the irradiated organism for the infectious virus [4, 12, 14, 21].

Thus when doses of virus are used which cause the death of almost 100% of the animals a comparatively large percentage of susceptible cells suffer, and therefore significant infiltrative--inflammatory changes are observed in tissues which are infected with virus. Here the determining factor is the effect of X-ray irradiation in the direction of reducing these changes, which in the final results indicates that there is a positive effect of radiation on the course of a virus infectious process. With the use of the same doses of viruses at which almost all the animals survive, a comparatively small percentage of susceptible cells turn out to be embraced by a specific pathological process. Under these conditions the determining factor is the effect of X-ray irradiation in the direction of intensifying the insemination of cells which are still not infected with virus (as a result of increasing the permeability of all the tissues of the irradiated organism for virus particles), which in combination with the immediate damaging effect of irradiation on cells which are infected with virus has as a final result a negative influence of radiation on the course of the infectious process.

The effect of irradiation on the infectious process depends to a considerable degree on the dose of virus: with a decrease in it an aggravating effect of ionizing radiation on the infectious process is observed, and with an increase in the dose of virus a "medicinal" effect of radiation is observed.

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